PATENT SPECIFICATION (11) 1270410

1270410

DRAWINGS ATTACHED

(21) Application No. 47314/69 (22) Filed 25 Sept. 1969
(45) Complete Specification published 12 April 1972
(51) International Classification A61K 27/00, 27/02, 27/06; A61L 13/00
(52) Index at acceptance
A5B 270 27Y 282 28Y 29X 29Y 38Y 390
A5E 1A1F3 1A1F4 1A1K 1A3E 1A3F 1A3G 1A5A2 1C12E 1C12G 1C12X 1C14 1C1D

(72) Inventors JOHN LORENA, G. RONARD ALUISY, NORMAN D. LOUD, and ROBERT H. RINES

(54) COLLOIDAL COMPOSITION AND METHOD OF PREPARING THE SAME

(71) We, ALLOR CORPORATION, a Corporation organized and existing under the laws of the State of Massachusetts, United States irradiated colloidal particulate heavy metals, appropriately combined in a suitable carrier, can accomplish remarkable bactericidal,

PATENTS ACT 1949

SPECIFICATION NO 1270410

The following corrections were allowed under Section 76 on 24 May 1972.

Substitute the following drawing for Fig 1, sheet 1.

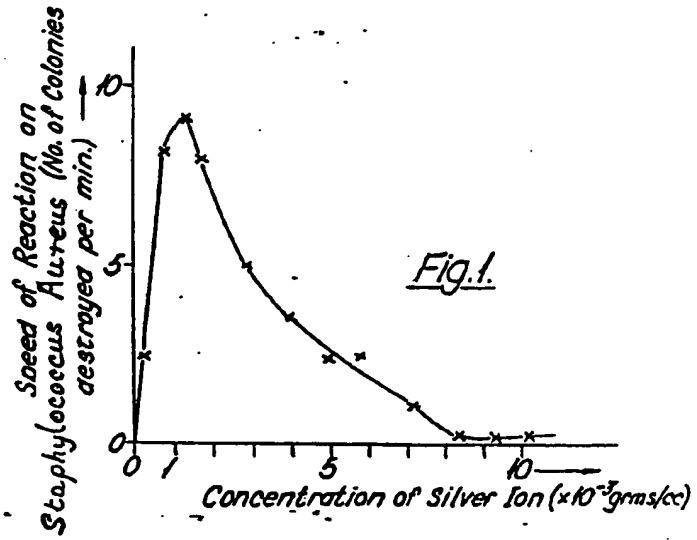

Fig.1.

THE PATENT OFFICE
5 July 1972

R 11025/:

SEE CORRECTION SLIP ATTACHED

PATENT SPECIFICATION (11) 1270410

1270410

DRAWINGS ATTACHED

(21) Application No. 47314/69 (22) Filed 25 Sept. 1969

(45) Complete Specification published 12 April 1972

(51) International Classification A61K 27/00, 27/02, 27/06; A61L 13/00

(52) Index at acceptance
A5B 270 27Y 282 28Y 29X 29Y 38Y 390
A5E 1A1F3 1A1F4 1A1K 1A3E 1A3F 1A3G 1A5A2 1C12E 1C12G 1C12X 1C14 1C1D

(72) Inventors JOHN LORINA, G. RONARD ALUISY, NORMAN D. LOUD, and ROBERT H. RINES

(54) COLLOIDAL COMPOSITION AND METHOD OF PREPARING THE SAME

(71) We, ALLOR CORPORATION, a Corporation organized and existing under the laws of the State of Massachusetts, United States of America, of The Gary Building, 4, Maple Street, Quincy, Massachusetts 02169, United States of America, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to colloidal compositions, and in a preferred embodiment to such compositions which have been irradiated; and methods of preparing the same. These compositions are particularly directed to killing bacteria and viruses and healing irritation; "irradiation" being used to mean exciting or charging by ultraviolet, gamma rays, X-rays, beta particles, neutrons, protons, deuterons and the like, but not long wavelength electromagnetic waves; the irradiated substances and compounds of the invention, however, having no detectable residual radioactivity.

While the art is replete with bactericides and disease-curing compounds of a wide variety of types, they all have limitations and disadvantages that restrict their safe or efficacious usage. As an illustration, *m*-cresol bactericide, widely used in hospitals and the like for clean rooms and to prevent contamination, requires a sufficiently strong concentration to be effective that it becomes irritating to the skin. Rather large doses of X-ray and other radiation have also been employed for bacteria and virus-killing and cancer and other disease-treatment or -curing purposes; but again such treatment is attendant upon disadvantages, including high radiation damage.

As explained in U.S. Application, Serial No. 749,141, underlying the present invention, in a preferred embodiment thereof, in summary, is the discovery that a small concentration, but above a second lower limit, of irradiated colloidal particulate heavy metals, appropriately combined in a suitable carrier, can accomplish remarkable bactericidal, irritation-dissipating and similar curative functions in such low concentrations as to itself be non-irritating, and, unlike X-rays, free of radioactivity and otherwise harmless to tissue and the like.

An object of the invention, accordingly, is to provide a new and improved irradiated composition and method or process of preparing and using the same that shall attain the above and other advantages.

Other objects are to provide novel noble heavy and transition metal chelates of bactericidal and medicinal efficacy.

Other and further objects will be hereinafter set forth.

The invention will now be described with reference to the accompanying drawing, Fig. 1 of which is an experimentally obtained graph illustrating the critical concentration discovery underlying the preferred form of the invention; and

Fig. 2 is a similar graph showing the relative kill efficacy upon *staphylococcus aureus*, *escherichea coli* and *b. subtilis* of a number of heavy and transition metals exhibiting the phenomenon underlying such discovery.

That discovery includes the finding that at very small concentrations, but above a second lower limit, colloidal particulate heavy and transition metals, such as the noble metals of Ag, Au, Pt, Pd, Rh, Ru, Cu, Cd, Re, Ti, Zr, Mo, Mn, Os, Ir, Tb, Pr, Ce, Th, Pa, U, Hf, W, V, Zn, Hg (and to rather minor extents Fe and Co) — all hereinafter generically referred to as the heavy and transition metals, the bulk of the metal present being in the form of colloidal particles in major proportion from 10^{-6} to 10^{-4} cm in size, can produce the novel results before summarized; while lesser or immediately greater concentrations do not function to achieve such results. As before stated,

SEE CORRECTION SLIP ATTACHED

ultra-violet, and electromagnetic radiation generators, for example of gamma and X-rays, have been found to be effective radioactivators or irradiators for the purposes of the invention; while electromagnetic radiation of longer wavelength than ultraviolet rays was not found to be effective.

EXAMPLE I

A colloidal silver suspension in a non-reactive water carrier solution, in which the particulate silver concentration is about 1.5 $\times 10^{-3}$ grams per cubic centimetre (or about 0.15% by weight) and the silver is irradiated as by a source of gamma radiation, has been found to provide remarkable bactericidal properties despite the miniscule proportion of the silver.

EXAMPLE II

A suspension is prepared as described in Example I and the silver is irradiated by X-ray radiation instead of by a source of gamma radiation.

Referring to Figure 1, the speed of reaction on *staphylococcus aureus* bacteria is plotted along the ordinate in units of colonies destroyed per minute, as a function of concentration of the silver ion, plotted in units of 10^{-3} grams per cubic centimetre along the abscissa. From these experimentally obtained data, it is evident that the before-mentioned concentration of about 1.5 $\times 10^{-3}$ grams per cubic centimetre is a critical and highly unexpected optimum concentration; lower concentrations, such as one-third the same, being inefficacious, as are higher concentrations, such as twice as much or greater. This critical concentration-destruction efficacy, moreover, was found to coincide, also, with what might be termed the measured optimum ionization constant (which involves the amount of freely conductive silver ions and the maximum chemical activity or optimum conductivity in a distilled water solution).

Using the standard Frost Little Plate method, a method of inspecting colonies of bacteria with a phase microscope and thereby observing breakdown of cell walls, a 50% kill of *staphylococcus aureus* was obtained with the above solution in about 4 minutes; and a 95% kill, in about 6 minutes.

As still another illustration with a different bacterium, said solution produced a 50% kill of *staphylococcus albus* in 7 minutes; and a 95% kill in about 9 minutes.

It is to be observed, moreover, that this miniscule colloidal particulate irradiated silver concentration is entirely harmless and non-irritating to the skin and free of radioactivity; and yet is comparable in its bactericidal properties to, for example, the widely used *m*-cresol, which, to the contrary, must be used in such strong concentration to be effective, that it is decidedly irritating to the user, and, indeed, precautions must be taken to prevent prolonged skin contact with the same.

It has further been found that the irradiation source, if of gamma rays or the like, need not exceed substantially 1.3 microcuries to produce the desired efficacious product.

EXAMPLE III

A silver chelate, formed with the alkaloids of the strychnine family (strychnine, brucine) or with a reserpine alkaloid in a non-toxic, non-reactive carrier solution have also been found most effective for the above and other purposes. At least part of the silver, in such concentration, remains dissociated from the chelate in colloidal, particulate form, which is believed to be the reason for its efficacy. The substantial maintenance of the particulate unclustered form is thus of importance. Specifically, a chelate of silver and strychnine, brucine and reserpine alkaloids, (the metal chelate ion being present in about the same before-mentioned concentration of 1.5 $\times 10^{-3}$ grams per cubic centimetre) combined in a water carrier was found to produce a slightly higher speed of kill as follows:

	Staphylococcus Aureus	*Staphylococcus Albus*
50% kill	3.5 min	6.2 min
95% kill	5.5 min	8.4 min

EXAMPLE IV

As still a further illustration, with the last-mentioned chelate present in a concentration of about 140 parts per million in an inert, non-reactive corn starch-water emulsion, similar bactericidal effects have been observed. In this chelate compound, the proportions of the strychnine and brucine alkaloids were about equal and about twice that of the reserpine alkaloid. In addition, the effective clearing up of acne and psoriasis has also been observed with this compound. Further, skin irritations (effected by needle stroking without leaving time for healing) that have been observed normally to develop skin cancer tumours (sarcoma) on guinea pigs, when periodically

covered by this compound (and despite continued needle stroking), progressively healed sufficiently that all indicia of the sarcoma disappeared. Other consistent healing effects have been observed.

Additional non-toxic systemic and topical carriers, non-reactive with the said critical concentration of radio-activated colloidal heavy metal being used (i.e. the silver, copper, gold or rhenium or other similar heavy or transition-type metal before listed, for example), have also been thus successfully employed, including ethanol, denatured with brucine; inert mineral oil; and an emulsion derived from borax and an aqueous solution.

An experimentally determined comparison between the particulate silver obtained from the silver chelate water solution (ultraviolet-irradiated and in the approximately 1.5×10^{-5} grams per cubic centimetre concentration) and a 6% solution of presently widely used hexachlorophene, showed the marked bactericidal superiority of the composition of the invention for several gram negative and positive bacteria, as follows:

Bacterium	Hexachlorophene		Silver chelate of Invention	
	% kill after 5 minutes	Maximum kill	% kill after 5 minutes	Maximum kill
Staphylococcus Aureus	50%	84%—48 hr	92%	100%— 8 min
Staphyloccocus Albus	57%	93%—48 hr	79%	100%—10 min
Escherichia Coli	58%	100%— 6 hr	88%	100%—10 min
P. Aeruginosa	70%	100%—25 min	85%	100%— 8 min
Candida Albicans	49%	94%—48 hr	80%	100%—30 min
Neisseria Catarrhalis	53%	100%—5 hr	90%	100%—10 min

The finely divided colloidal particles in the substances and compounds of the invention have been found to have a large number (in fact, in some measurements, 50% or more) of separate particles of size range between substantially 10^{-5} and 10^{-4} cm. (in some measurements the average size being in this range), which are believed to be important for the cell penetration or other effects herein involved. Similarly dimensioned silver particles alone, not derived from chelates, but irradiated with X-rays (gamma), as before described, have also been found to produce substantial bactericidal and healing effects; to wit, such irradiated colloidal silver in water solution in the above-mentioned concentration produced a 93% kill of *staphylococcus aureus* in five minutes, and a 91% kill of *staphylococcus albus* in the same period with 100% kill in about ten minutes. This is as compared with only relatively slight kills for the same silver colloidal particles, non-irradiated — which, though of some use in certain applications, are not nearly as efficacious as the irradiated particles.

Similarly, each of, for example, irradiated copper, gold, platinum, iridium, manganese, and rhenium colloidal particles of the same size range, have been proven effective as bactericides, producing kills of the same above-listed bacteria. Theoretically this would appear to apply to all heavy and transition-type metals, so prepared, though the efficacy will vary with the element. Substantially the same approximately 1.5×10^{-5} grams per cubic centimetre low-concentration optimum constant of the silver particles, for example, was found to exist for gold, rhenium and copper colloidal particles, with gold being much more efficacious in time of kill, as indicated in Fig. 2. In the tests shown in Fig. 2, moreover, rhenium proved more efficacious than silver, and copper showed a remarkable efficacy for greater concentrations beyond the low-concentration optimum. Other tested irradiated metals that also show this same substantially 1.5×10^{-5} grams/c.c. constant include the before-listed Ti, Zr, Mo, Mn, Ru, Rh, Pd, Os, Ir, Pt, Tb, Pr, Ce, Th, Pa, U, Hf, W, V, Zn, Cd and Hg.

Other ultraviolet-irradiated inorganic chelate compounds (including sunlight-irradiated) with particulate heavy and transition metal ions found to be bactericidal in water solution of the above-mentioned concentration are alkaloidal solutions (containing brucine, strychnine and colchinine alkaloids)

having trace metals of copper and thallium. These proved to be effective against each of *escherichia coli, staphylococcus aureus* and *bacillus subtilis.*

Among the healing effects, before-mentioned, is the unbelievably rapid reduction in burn histamine-type pain response, erythema and redness, and absence of blister, all effected with boil oil and water suspensions of each, for example, of the silver, gold, copper and, to a lesser extent, rhenium colloidal particulate metals before tested as bactericides.

While an invention may be defined in terms of the process, products, and results, it sometimes aids in understanding to theorize as to the possible operation; though it is distinctly to be understood that the present invention is not dependent upon theories, whether accurate or inaccurate. It appears likely, however, that the apparently universal nature of the bactericidal substances of the invention (no bacteria yet tried has not been rapidly killed) may reside in the supplying of appropriately small, unclustered and free heavy metal ions (probably freed by the irradiation or otherwise similarly electrically charged to prevent clustering) that, by induced electron exchange, effect a change (probably a reduction), either catalytically or by chemical combination, in the intracellular oxygen and peroxides generated at or in the vicinity of the cell. In the case of pathogenic organisms, this appears to debilitate and destroy the same.

Evidence of further universality has been obtained in the efficacy of, for example, the silver compounds of the invention, against virus such as cow-pox and cold virus.

Concurrently, in the case of animal and human cells, this phenomenon also appears to control the metabolic rate through the oxygen and peroxide control or anti-oxidant activity or the like, possibly replacing such metal ions at the cells that may have been chemically combined or consumed by disease, radiation or other damage (or, in the case of prevention, that may subsequently be consumed, combined or rendered ineffective). It is an observable fact, however, that a type of healing and unusually rapid outward growth of light pink tissue occurs, void of the usual scabbing and inward slow-healing provided by nature, in diseased, cut and damaged tissue treated with the substances of the invention. It would appear that the substances of the invention, whether externally or systemically applied, act within the enzymic system to improve cellular efficiency and healing. Differentiation in action upon strong and weak or diseased cells has been observed in the before-mentioned preliminary cancer studies; it being plausible that either replacement of unsubstituted carbon in benzene ring chains that are carcinogenic in the absence of such substitution, by the readily active freed or free-radical heavy metal ions in the compounds of the invention, or reconstituting of the metabolic oxygen-control or similar process (or both), is an explanation for the observed phenomena. (See, for example, "Chemical Basis of Carcinogenic Activity", G. M. Badger, 1962, p. 23).

Apart from the noble metals, an interesting observation appears to be, moreover, that the transition metals above-listed can have a coordination or valence number 4, capable of electron transitions or resonances between the second and third electron orbits. This may account for the apparently universal 1.5×10^{-3} constant previously discussed — the bacteria, all being of substantially the same range of dimensions, perhaps being electromechanically destroyed by such oscillations.

These compounds of the present invention, moreover, have been preliminarily found to assist rather startlingly in the slowing or inhibiting of certain processes associated with ageing; specifically, the continual application on a daily basis of an oil dispersion of particulate irradiated silver in the said optimum concentration, as before discussed, has been found to prevent cornification of the skin in cases of ichthyosis wherein a rapid localized ageing takes place as a result of the rapid cellular death rate involved in cornification of the skin.

Another element generally associated with the ageing process is the development of wrinkles accompanying the breakdown of the connective tissue layers of the skin, with resulting loss of elasticity. Such breakdown has been observed to become halted through similar application of the said compounds of the invention.

And, still another example of a further element associated with the ageing process that has been found to become obviated through the application of the first-named water solution of the irradiated particulate silver (in the said optimum concentration), is non-infective seborrhea of the scalp involving an acceleration of cellular death rate. The use of such water solution has been found to result in the marked decrease in the index of cebrial activity.

While, moreover, the optimum concentration effect shown in the drawing is obviously highly desirable from considerations of economy and possible toxicity, it does prevent continued efficacy upon substantial dilution of the solution. For such purposes and others, accordingly, the solutions may be substantially more concentrated or saturated, as shown to the far right in Fig. 2 (and beyond), though the bactericidal and healing effects do not, except in the case of the particular copper tests indicated, appear to exceed those obtainable with the minimal optimum concentration (and in many cases, do not reach the same peak of performance). To permit such dilution to the order of 1/100, without dropping the efficacy more than about 12%, a practical use concen-

tration of the heavy or transition metal ion-chelate may seemingly be from 10—15% (by weight) for a useful commercial or economic (diminishing marginal return) range.

In the case of irradiated chelates, there appear to be instances where the metal does not sufficiently dissociate therefrom to control the above effects as the colloidal particulated free metal, and where efficacy increases with concentration on a substantially continual basis, Chelates in which the metal ion is of coordination number 1 seem to fall within this category. For example, chelates of mercurous, cuprous, silver and aurous compounds have shown highly increased bactericidal kill effects (against *staphylococcus aureus, e. coli* and *b. subtilis*) with about a 4% concentration. Included in these irradiated chelates (which do not appear to produce these results in the absence of irradiation) are tetraammine Cu II, bis-ethylenediamine Au II, hexacyanomanganate and hexachlororheniate, all of which have excellent bactericidal properties at this 4% concentration and above.

WHAT WE CLAIM IS:—

1. Bactericidal compositions comprising, as active ingredient, at least one metal, dispersed in a carrier solution non-reactive to the metal, the bulk of the metal present being of substantially colloidal particle size, and in which said metals are selected from Pt, Pd, Rh, Cu, Ru, Os, Ir, Tb, Pr, Ce, Th, Pa, U, Hf, W, V, Re, Zn, Cd, Hg, Au, Ag, and the colloidal particles are in major proportion from 10^{-5} to 10^{-6} cm. in size.

2. A composition as claimed in Claim 1 and in which the said particles have been previously irradiated.

3. A composition as claimed in Claim 1 and in which the particles are substantially unclustered in the said particulate form.

4. A composition as claimed in Claim 3 and in which the particles are maintained in their unclustered condition by virtue of being electrically charged.

5. A composition as claimed in Claim 1 and in which the metal concentration is substantially 1.5×10^{-3} grams per cubic centimetre.

6. A composition as claimed in Claims 2 and 5 comprising silver in colloidal particlate form.

7. A process for controlling the growth and proliferation of bacteria in living cells and tissue other than of humans, which comprises applying to a site in or on living cells or tissue and infested, or susceptible to infestation, with bacteria at least one composition as claimed in Claim 1.

8. A process as claimed in Claim 7 and in which the particles have been maintained unclustered in the said colloidal form by irradiation, whereby the composition is as claimed in Claim 2.

9. A process as claimed in Claim 7 and in which the said applying step is periodically repeated until at least one of bacteria- and virus-killing, irritation- and disease-dissipation, healing, and inhibiting of ageing, occurs.

10. A process for controlling the growth and proliferation of bacteria in *living cells and tissue* other than of humans, which comprises applying to a site in or on *living cells and tissue* and infested, or susceptible to infestation, with bacteria at least one composition as claimed in Claims 2 and 5.

11. A composition as claimed in either of Claims 1 or 6 and in which the metal or metals are present in a chelate formed with at least one alkaloid of the strychnine family or a reserpine alkaloid which is in part dissociated into the metal or metals and the chelating compounds.

12. A composition as claimed in Claim 1 or Claim 6 wherein the metal or metals are present in a chelate formed with at least one brucine alkaloid.

13. A composition as claimed in Claim 11 and in which said carrier is one suitable for topical application.

14. A composition as claimed in Claim 11 and in which said carrier is one suitable for systemic administration.

15. A process for preparing a bactericidal composition comprising, as active ingredient, at least one metal selected from Pt, Pd, Rh, Cu, Ru, Os, Ir, Tb, Pr, Ce, Th, Pa, U, Hf, W, V, Re, Zn, Cd, Hg, Au, or Ag suspended in a carrier solution non-reactive to the metal, the bulk of the metal present being in the form of colloidal particles in major proportion from 10^{-5} to 10^{-6} cm in size: which comprises suspending the colloidal particulate metal in a carrier non-reactive to the metal, adjusting the concentration of said metal to substantially 1.5×10^{-3} grams per cubic centimetre, and irradiating the suspended metal so as to produce a composition as claimed in Claims 2 and 5.

16. A process as claimed in Claim 15 and in which said irradiating step is carried out by gamma-ray or X-ray radiation, the irradiation source being at about 1.3 microcuries.

17. A process as claimed in Claim 15 in which the composition produced is as claimed in Claim 12.

18. An irradiated chelate of a metal selected from Pt, Pd, Rh, Cu, Ru, Os, Ir, Tb, Pr, Ce, Th, Pa, U, Hf, W, V, Re, Zn, Cd, Hg, Au, Ag in aqueous solution in which the concentration of metal chelate ion is selected from values of substantially 1.5×10^{-3} grams per cubic centimetre and the range of from 8.3% to 15%, based on the total weight of the solution; which solution contains colloidal particles, in major proportion from 10^{-5} to 10^{-6} cm in size.

19. Bactericidal compositions comprising, as active ingredient, at least one irradiated particulate heavy metal selected from the group consisting of Hg, Au, and Cu, in which metal the average particle size is in the range of from

10^{-5} to 10^{-4} cm, and in which composition the particle concentration is selected from values of substantially 1.5×10^{-4} grams per cubic centimetre and the range of from substantially 8.3% to 15% by weight.

20. Compositions as claimed in Claim 2 comprising, as active ingredient, at least one metal as claimed in Claim 19.

21. An irradiated particulate as claimed in Claim 19 and in which the particles are colloidally suspended in a carrier non-reactive with the metal.

22. Compositions as claimed in Claim 18 comprising, as active ingredient, at least one metal as defined in Claim 18 combined in a non-reactive carrier.

CLEVELAND AND JOHNSON,
Chartered Patent Agents,
Agents for the Applicants,
Chancery House,
Chancery Lane,
London, WC2A 1QU.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1972.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

1270410 COMPLETE SPECIFICATION

1 SHEET

This drawing is a reproduction of the Original on a reduced scale

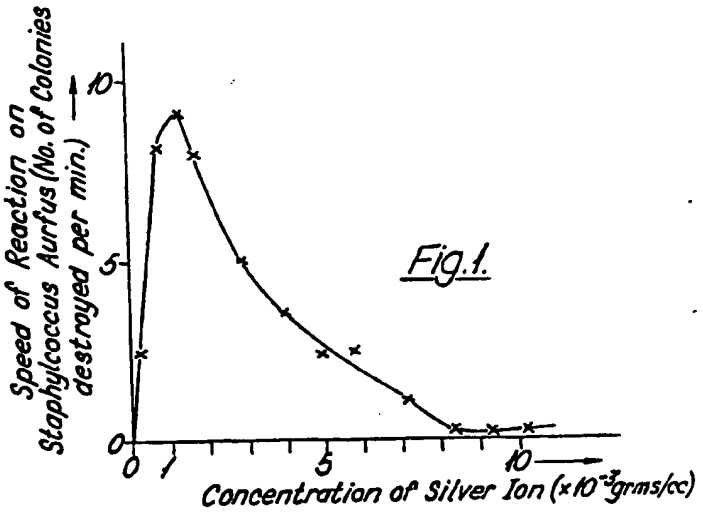

Fig.1.

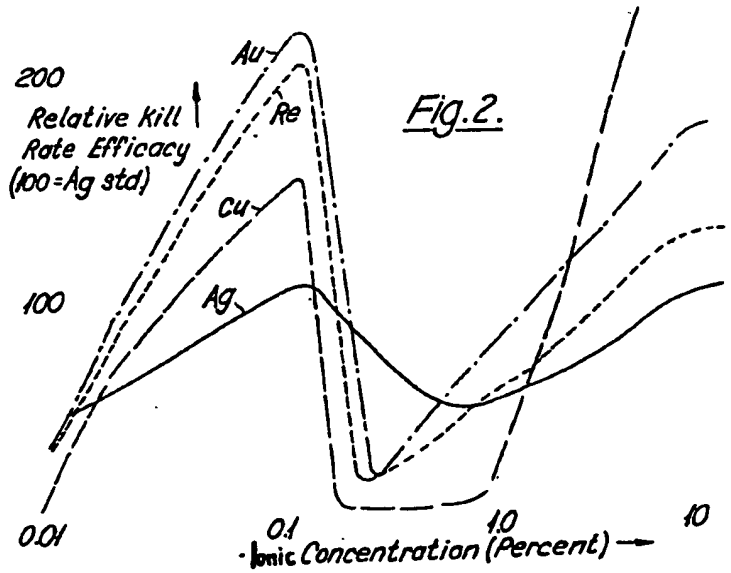

Fig.2.